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SYNTHESIS OF *N*-(1-ETHYL-4-METHYLHEXAHYDRO-1,4-DIAZEPIN-6-YL)NICOTINAMIDES AND THEIR AFFINITIES FOR 5-HT_3 AND DOPAMINE D_2 RECEPTORS

Yoshimi Hirokawa,* Naoyuki Yoshida and Shiro Kato

Discovery Research Laboratories I, Dainippon Pharmaceutical Co., Ltd., Enoki 33-94, Suita, Osaka 564-0053, Japan

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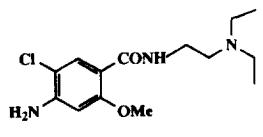
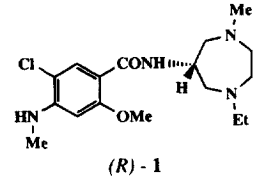
Abstract: A series of *N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)nicotinamide derivatives were prepared and evaluated for their binding to 5-HT_3 and dopamine D_2 receptors. Among them, the 5-bromo-2-methoxy-6-methylaminonicotinamide **16** and its (*R*)-isomer were found to have potent affinities for both receptors. The affinities of (*R*)-**16** for 5-HT_3 and dopamine D_2 receptors are approximately 3-fold higher than those of the corresponding benzamide (*R*)-**1** (IC_{50}: 1.1 and 12 nM *vs.* 2.9 and 35 nM, respectively).

In a preceding paper, we reported that, in a series of novel benzamide derivatives with a hexahydro-1,4-diazepine ring in the amine moiety, (*R*)-5-chloro-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-4-methylaminobenzamide [(*R*)-**1**] was a potent dual antagonist for serotonin-3 (5-HT_3) and dopamine D_2 receptors.[1] The affinities (5-HT_3 receptor; IC_{50}: 2.9 nM, D_2 receptor; IC_{50}: 35 nM) were significantly higher than those of metoclopramide (5-HT_3 receptor; IC_{50}: 880 nM, D_2 receptor; IC_{50}: 480 nM). Moreover, we continued to search



metoclopramide



(*R*) - **1**

compounds with more potent antagonistic activities for 5-HT_3 and dopamine D_2 receptors. Recently, Coldwell *et al.* demonstrated that 6-amino-5-chloro-2-methoxynicotinoyl group is a viable bioisostere for the 4-amino-5-chloro-2-methoxybenzoyl moiety of the benzamides with 5-HT_3 or dopamine D_2 receptor antagonistic activity.[2] Therefore, it was expected that replacement of the benzoyl group of the *N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)benzamides by a corresponding nicotinoyl group would result in retention of the affinities for 5-HT_3 and dopamine D_2 receptors. In this communication, we describe the preparation of the 2,5,6-trisubstituted nicotinamides **13**–**18** and structure-activity relationships (SARs) concerning their 5-HT_3 and dopamine D_2 receptor affinities.

Chemistry

According to the method of Coldwell *et al.*,[2] the intermediate, methyl 6-amino-2-methoxynicotinate (**4**), was prepared from 2,6-difluoropyridine (**2**) *via* the 2-fluoronicotinic ester **3**. Chlorination of **4** with *N*-

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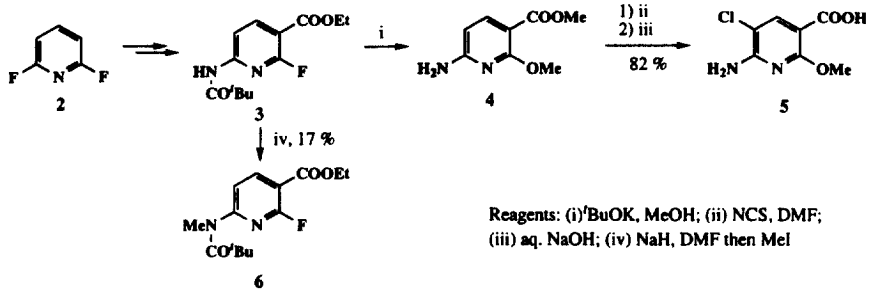
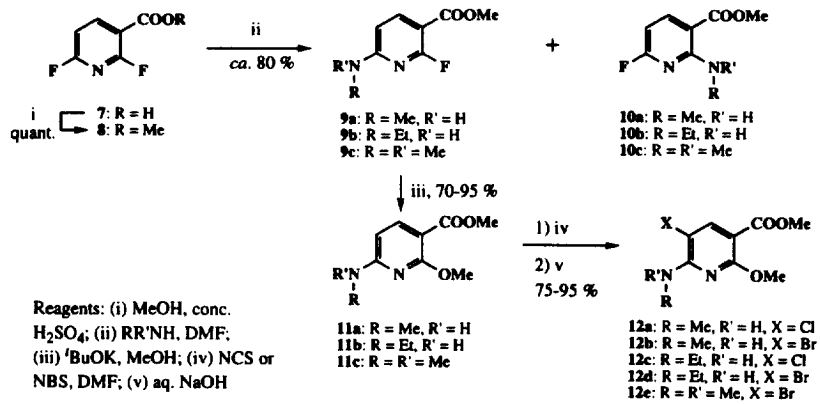
chlorosuccinimde (NCS) in DMF, followed by alkaline hydrolysis of the resulting 5-chloronicotinic ester afforded the nicotinic acid **5** in 82% yield. The preparation of the 6-alkylaminonicotinic acids was next examined. First, *N*-methylation of **3** was tried, but the expected *N*-methylnicotinic ester **6** was only 17% yield (Scheme 1). Thus, the reaction of methyl 2,6-difluoronicotinate (**8**) with methylamine was carried out.

Scheme 1



Treatment of **8** prepared from the nicotinic acid **7**[3] with methylamine below 5 ℃ in DMF afforded a mixture of the desired 6-methylaminonicotinic ester **9a** and the regioisomer **10a** in 86% yield in a ratio of 2:1. The reaction of **8** with ethylamine and dimethylamine was performed under similar conditions to the ones described above to give a mixture of **9b,c** and **10b,c** in *ca.* 80 % yield. The mixture of **9a-c** and **10a-c** was conveniently separated by recrystallization or column chromatography on silica gel.[4] The structures of **9a-c** and **10a-c** were confirmed by the nuclear Overhauser effects (NOEs); in the difference NOE spectra of **9a-c**, irradiations of the *N*-alkyl groups enhanced the signal intensities of the protons at the 5-position in pyridine ring. However, NOEs of **10a-c** were not observed at the protons in the pyridine ring on irradiation of *N*-alkyl groups. The nicotinic esters **9a-c** were treated with potassium methoxide which was generated from methanol and potassium *tert*-butoxide to give the 2-methoxynicotinic esters **11a-c** in good yields. Reaction of **11a-c** with NCS or NBS in DMF, followed by alkaline hydrolysis afforded the nicotinic acids **12a-e** in good yields (Scheme 2).

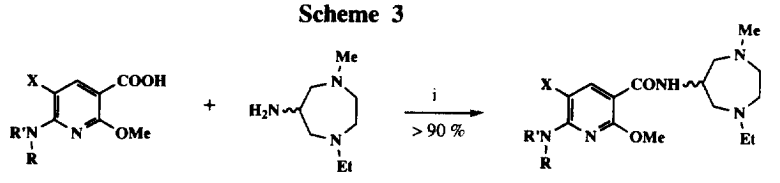
Scheme 2



Condensation of the nicotinic acids **5** and **12a-e** thus obtained with 6-amino-1-ethyl-4-methylhexahydro-1,4-diazepine[1] in presence of *N,N'*-carbonyldiimidazole produced the racemic nicotinamides **13**−**18** in over

90 % yield, and the optically active nicotinamides [(*R*)-**14**, (*S*)-**14**, (*R*)-**16** and (*S*)-**16**] were prepared in a similar manner (Scheme 3).

Scheme 3



5, 12a-e **13-18, (*R*)-14, (*S*)-14, (*R*)-16, (*S*)-16**

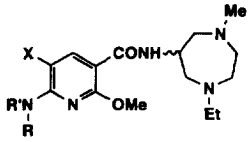
Reagent: (i) *N,N'*-carbonyldiimidazole, DMF

Results and discussion

The affinities of the *N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)nicotinamides **13**−**18**, (*R*)-**14**, (*S*)-**14**, (*R*)-**16** and (*S*)-**16** listed in Table 1 were determined using binding assays; for 5-HT_3 receptors, competition for [^{3}H]GR65630 binding site in rat cortical membranes[5] was used, while the affinity for dopamine D_2 receptors was evaluated with [^{3}H]spiperone in rat striatum.[6] For comparison, data for (*R*)-**1** and metoclopramide were included in Table 1.

Most of the nicotinamides **13**−**18** prepared showed high affinity for 5-HT_3 receptors with IC_{50} values between 1.0 nM to 9.9 nM and moderate to high affinity for dopamine D_2 receptors. The 6-aminonicotinamide

Table 1. 5-HT_3 and Dopamine D_2 Receptor Affinities for *N*-(1-Ethyl-4-methylhexahydro-diazepin-6-yl)nicotinamide Derivatives



Compd.[a]	R	R'	X	Binding Assay: IC_{50} (nM) Dopamine D_2[b]	5-HT_3[c]
13	H	H	Cl	386	5.1
14	Me	H	Cl	43	1.3
15	Et	H	Cl	76	2.0
16	Me	H	Br	23	1.0
17	Et	H	Br	48	3.8
18	Me	Me	Br	75	9.9
(*R*)-**14**[d]	Me	H	Cl	18	1.6
(*S*)-**14**[d]	Me	H	Cl	202	2.1
(*R*)-**16**[d]	Me	H	Br	12	1.1
(*S*)-**16**[d]	Me	H	Br	81	1.2
		(*R*)-**1**[e]		35	2.9
		metoclopramide		480	880

a) All compounds gave satisfactory results on IR, ^{1}H-NMR, MS and elemental analysis. *b*) Determined in rat brain synaptic membranes using [^{3}H]spiperone. *c*) Determined in rat cortical membranes using [^{3}H]GR65630. *d*) The enantiomeric purities of the enantiomers were confirmed to be >98% ee by HPLC [column; CHIRALPAK AS (DAICEL Chemical Industries Ltd., Japan)]. *e*) See ref.1

13 was found to show a strong affinity for 5-HT_3 receptors and to be almost equipotent to metoclopramide in affinity for dopamine D_2 receptors. Influence of substituents on the 6-amino group of the nicotinoyl moiety of **13** was first examined. Introduction of a methyl group (giving **14**) led to a significant increase in affinity for dopamine D_2 receptors. The affinity for 5-HT_3 receptors of **14** was essentially 4-fold higher than that of **13**. A similar result has previously been observed with the corresponding benzamide.[1] The ethyl substituent **15** slightly decreased the 5-HT_3 and dopamine D_2 receptor affinities compared with those of **14**. Next, the influence of the 5-substituent was studied. Replacement of the chlorine atom of **14** by a bromine atom (yielding **16**) led to an enhancement in affinity for dopamine D_2 receptors. The affinity of **16** for dopamine D_2 receptors was *ca.* 2-fold higher than that of **14** and for 5-HT_3 receptors, it was approximately equipotent to **14**. The both affinities of the 6-ethylamino derivative **17** and the 6-dimethylamino derivative **18** were lower than those of **16**. As a result of the SARs described above, the optimum substituent at the 5- and 6-positions of the pyridine ring was concluded to be bromo and methylamine groups, respectively. Finally, the affinities for 5-HT_3 and dopamine D_2 receptors of the enantiomers of **14** and **16** were examined. The affinities for dopamine D_2 receptors of the *R*-enantiomers of **14** and **16** [(*R*)-**14** and (*R*)-**16**] were *ca.* 2-fold higher than those of the racemates **14** and **16**, whereas their affinities for 5-HT_3 receptors were approximately similar. Their *S*-enantiomers showed weak affinity for dopamine D_2 receptors, but retained strong affinity for 5-HT_3 receptors. Thus, it was found that the affinity for dopamine D_2 receptors separated in each enantiomer, and the only *R*-enantiomer showed potent affinity. The affinities for 5-HT_3 and dopamine D_2 receptors of (*R*)-**16**[7] were *ca.* 3-fold higher than those of (*R*)-**1** [IC_{50}: 12 nM *vs.* 35 nM and 1.1 nM *vs.* 2.9 nM].

In conclusion, conversion of benzoyl moiety of (*R*)-**1** to nicotinoyl moiety increased the affinities for 5-HT_3 and dopamine D_2 receptors. Overall, (*R*)-**16** was selected as a dual antagonist for both receptors.

References and Notes

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4. ^{1}H-NMR (200 MHz, $CDCl_3$); **9a**: δ 2.98 (d, 3H, J = 6 Hz), 3.87 (s, 3H), 5.49 (br s, 1H), 6.24 (dd, 1H, J = 2.0, 8.5 Hz), 8.09 (dd, 1H, J = 8.5, 9.5 Hz). **10a**: δ 3.03 (d, 3H, J = 5 Hz), 3.85 (s, 3H), 6.07 (dd, 1H, J = 3.0, 8.5 Hz), 8.12 (br, 1H), 8.18 (t, 1H, J = 8.5 Hz).
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7. Data of (*R*)-**16** (difumarate): mp 152 − 153 ℃ (EtOH); ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.02 (t, 3H, J = 7 Hz), 2.43 (s, 3H), 2.5-3.0 (10H, m), 2.93 (d, 3H, J = 5 Hz), 3.98 (s, 3H), 4.14 (m, 1H), 6.60 (s, 4H), 6.99 (d, 1H, J = 5 Hz), 8.09 (s, 1H), 12.80 (br s); Chiral HPLC (CHIRALPAK AS), t_R = 23.7 min [(*S*)-**16**: t_R = 27.4 min]. To determine *in vivo* 5-HT_3 and dopamine D_2 receptor antagonistic activities of (*R*)-**16**, inhibition of 2-methyl-5-HT-induced bradycardia (von Bezold-Jarisch reflex) in rats[8] (ED_{50}; 2.3 μg/kg, iv) and of apomorphine-induced emesis in dogs[9] (ED_{50}; 0.07 mg/kg, po), respectively, were examined.
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